IN THE SPECIFICATION

Kindly amend the specification as follows*:

On page 2, replace the first full paragraph under "Continuing Application Data" with the following:

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The instant utility application claims priority to U.S. provisional patent application number 60/103,418, filed on October 7, 1998, the entire contents of which is incorporated herein by reference; and the instant application is related to co-pending utility applications U.S.S.N. 09/374,958 and 09/374,936 (Attorney Docket Nos. STK-076 and STK-077) filed on even date herewith and also based on the aforementioned provisional application, the disclosures of which are incorporated herein by reference.

On page 24, replace the brief description of figure 4 with the following:

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Figure 4 lists the aligned C-terminal residues defining the finger 2 sub-domain for various known members of the BMP family, and TGF-β superfamily of proteins, starting with the first residue following the cysteine doublet. OP-1 (amino acid residues 66-102 of SEQ ID NO: 55); BMP-5 (amino acid residues 66-102 of SEQ ID NO: 52); BMP-6 (amino acid residues 66-102 of SEQ ID NO: 53); OP-2 (amino acid residues 66-102 of SEQ ID NO: 56); OP-3 (amino acid residues 66-102 of SEQ ID NO: 57); 60A (amino acid residues 82-118 of SEQ ID NO: 48); Vg-1 (amino acid residues 66-102 of SEQ ID NO: 46); Univin (amino acid residues 1-35 of SEQ ID NO: 34); BMP-2 (amino acid residues 66-102 of SEQ ID NO: 49); BMP-4 (amino acid

* An "Appendix of Amendments" is enclosed as Exhibit A, showing the amendments to the specification and claims. In that Appendix, the added portions are underscored and the deleted portions are bracketed.

residues 65-101 of SEQ ID NO: 51); GDF-5 (amino acid residues 66-102 of SEQ ID NO: 83); GDF-6 (amino acid residues 66-102 of SEQ ID NO: 85); GDF-7 (amino acid residues 66-102 of SEQ ID NO: 87); CDMP-2 (amino acid residues 66-102 of SEQ ID NO: 86); DPP (amino acid residues 66-102 of SEQ ID NO: 45); BMP-9 (amino acid residues 1-35 of SEQ ID NO: 7); Dorsalin (amino acid residues 66-103 of SEQ ID NO: 54); BMP-10 (amino acid residues 1-35 of SEQ ID NO: 8); GDF-3 (amino acid residues 65-101 of SEQ ID NO: 59); GDF-1 (amino acid residues 71-107 of SEQ ID NO: 58); SCREW (amino acid residues 1-35 of SEQ ID NO: 28); BMP-3 (amino acid residues 67-103 of SEQ ID NO: 50); NODAL (amino acid residues 1-34 of SEQ ID NO: 25); TGF-β1 (amino acid residues 63-98 of SEQ ID NO: 40); TGF-β2 (amino acid residues 63-98 of SEQ ID NO: 41); TGF-β3 (amino acid residues 63-98 of SEQ ID NO: 42); TGF-β4 (amino acid residues 63-98 of SEQ ID NO: 43); TGF-β5 (amino acid residues 63-98 of SEQ ID NO: 44); GDF-5 (amino acid residues 63-98 of SEQ ID NO: 40); Inhibin α (amino acid residues 66-105 of SEQ ID NO: 61); Inhibin βA (amino acid residues 70-106 of SEQ ID NO: 62); Inhibin βB (amino acid residues 70-106 of SEQ ID NO: 63); Inhibin βC (amino acid residues 1-35 of SEQ ID NO: 23); MIS (amino acid residues 1-34 of SEQ ID NO: 24); GDNF (amino acid residues 1-32 of SEQ ID NO: 19); BMP-11 (amino acid residues 1-35 of SEQ ID NO: 9); GDF-9 (amino acid residues 66-102 of SEQ ID NO: 60).

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On page 25, replace the brief description of figure 5 with the following:

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Figures 5A, 5B, and 5C are sequence alignments using single letter amino acid code, arranged to indicate alignments and homologies of the finger 1, heel, and finger 2 regions, respectively, of the currently known

members of the TGF-β superfamily. Shown are the respective amino acids comprising each region of human TGF-β1 through TGF-β5 (the TGF-β subgroup), the Vg/dpp subgroup consisting of dpp, Vg-1, Vgr-1, 60A (see copending U.S.S.N. 08/271,556), BMP-2A (also known in the literature as BMP-2), dorsalin, BMP-2B (also known in the literature as BMP-4), BMP-3, BMP-5, BMP-6, OP-1 (also known in the literature as BMP-7), OP-2 (see PCT/US91/07635 and U.S. Patent No. 5,266,683) and OP-3 (U.S.S.N 07/971,091), the GDF subgroup consisting of GDF-1, GDF-3, and GDF-9, the Inhibin subgroup consisting of Inhibin α, Inhibin βA, and Inhibin βB. The dashes (-) indicate a peptide bond between adjacent amino acids. A consensus sequence pattern for each subgroup is shown at the bottom of each subgroup. In Figure 5A the finger 1 sequences correspond to the following SEQ ID NOS: TGF-β1 (residues 1-34 of SEQ ID NO:40); TGF-β2 (residues 1-34 of SEQ ID NO:41); TGF-β3 (residues 1-34 of SEQ ID NO:42); TGF-β4 (residues 1-34 of SEQ ID NO:43); TGF-β5 (residues 1-34 of SEQ ID NO:44); TGF-* pattern (1-34 of SEQ ID NO: 64); dpp (residues 1-34 of SEQ ID NO:45); Vg-1 (residues 1-34 of SEQ ID NO:46); Vgr-1 (residues 1-34 of SEQ ID NO:47); 60A (residues 1-34 of SEQ ID NO:48); BMP-2A (residues 1-34 of SEQ ID NO:49); DORSALIN (residues 1-34 of SEQ ID NO:54); BMP-2B/BMP-4 (residues 1-34 of SEQ ID NO: 51); BMP-3 (residues 1-34 of SEQ ID NO: 50); BMP-5 (residues 1-34 of SEQ ID NO:52); BMP-6 (residues 1-34 of SEQ ID NO:53); OP-1/BMP-7 (residues 1-34 of SEQ ID NO:55); OP-2 (residues 1-34 of SEQ ID NO:56); OP-3 (residues 1-34 of SEQ ID NO:57); Vg/dpp subgroup pattern (residues 1-34 of SEQ ID NO:65); GDF-1 (residues 1-34 of SEQ ID NO:58); GDF-3 (residues 1-34 of SEQ ID NO:59); GDF-9 (residues 1-34 of SEQ ID NO:60); GDF subgroup pattern (residues 1-34 of SEQ ID NO:66); Inhibin α (residues 1-34 of SEQ ID NO:61); Inhibin βA (residues

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1-34 of SEQ ID NO:62); Inhibin βB (residues 1-34 of SEQ ID NO:63); Inhibin subgroup pattern (residues 1-34 of SEQ ID NO:67).

In Figure 5B the heel sequences correspond to the following SEQ ID NOS: TGF-β1 (residues 35-64 of SEQ ID NO:40); TGF-β2 (residues 35-64 of SEQ ID NO:41); TGF-β3 (residues 35-64 of SEQ ID NO:42); TGF-β4 (residues 35-64 of SEQ ID NO:43); TGF-β5 (residues 35-64 of SEQ ID NO:44); TGF-β pattern (residues 35-64 of SEQ ID NO: 64); dpp (residues 35-67 of SEQ ID NO:45); Vg-1 (residues 35-67 of SEQ ID NO:46); Vgr-1 (residues 35-67 of SEQ ID NO:47); 60A (residues 35-67 of SEQ ID NO:48); BMP-2A (residues 35-66 of SEQ ID NO:49); DORSALIN (residues 35-67 of SEQ ID NO:54); BMP-2B/BMP-4 (residues 35-66 of SEQ ID NO: 51); BMP-3 (residues 35-68 of SEQ ID NO: 50); BMP-5 (residues 35-67 of SEQ ID NO:52); BMP-6 (residues 35-67 of SEQ ID NO:53); OP-1/BMP-7 (residues 35-67 of SEQ ID 35-67 of SEQ ID NO:57); Vg/dpp subgroup pattern (residues 35-68 of SEQ ID NO:65); GDF-1 (residues 35-72 of SEQ ID NO:58); GDF-3 (residues 35-66 of SEQ ID NO:59); GDF-9 (residues 35-67 of SEQ ID NO:60); GDF subgroup pattern (residues 35-72 of SEQ ID NO:66); Inhibin α (residues 35-67 of SEQ ID NO:61); Inhibin βA (residues 35-71 of SEQ ID NO:62); Inhibin βB (residues 35-71 of SEQ ID NO:63); Inhibin subgroup pattern (residues 35-71 of SEQ ID NO:67).

In Figure 5C the finger 2 sequences correspond to the following SEQ ID NOS: TGF-β1 (residues 65-98 of SEQ ID NO:40); TGF-β2 (residues 65-98 of SEQ ID NO:41); TGF-β3 (residues 65-98 of SEQ ID NO:42); TGF-β4 (residues 65-98 of SEQ ID NO:43); TGF-β5 (residues 65-98 of SEQ ID NO:44); TGF-β pattern (residues 65-98 of SEQ ID NO: 64); dpp (residues 68-102 of SEQ ID NO:45); Vg-1 (residues 68-102 of SEQ ID NO:46); Vgr-1 (residues 68-102 of SEQ ID NO:47); 60A (residues 68-102 of SEQ ID NO:48); BMP-2A

(residues 68-102 of SEQ ID NO:49); DORSALIN (residues 68-103 of SEQ ID NO:54); BMP-2B/BMP-4 (residues 68-102 of SEQ ID NO: 51); BMP-3 (residues 68-102 of SEQ ID NO: 50); BMP-5 (residues 68-102 of SEQ ID NO:52); BMP-6 (residues 68-102 of SEQ ID NO:53); OP-1/BMP-7 (residues 68-102 of SEQ ID NO:55); OP-2 (residues 68-102 of SEQ ID NO:56); OP-3 (residues 68-102 of SEQ ID NO:57); Vg/dpp subgroup pattern (residues 68-103 of SEQ ID NO:65); GDF-1 (residues 73-107 of SEQ ID NO:58); GDF-3 (residues 67-101 of SEQ ID NO:59); GDF-9 (residues 68-102 of SEQ ID NO:60); GDF subgroup pattern (residues 73-107 of SEQ ID NO:66); Inhibin α (residues 68-105 of SEQ ID NO:61); Inhibin βA (residues 72-106 of SEQ ID NO:62); Inhibin βB (residues 72-106 of SEQ ID NO:63); Inhibin subgroup pattern (residues 72-109 of SEQ ID NO:67).

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On page 25, replace the brief description of figure 6 with the following:

Figure 6 is a single letter code listing of amino acid sequences, identified in capital letter in standard single letter amino acid code, and in lower case letters to identify groups of amino acids useful in that location, wherein the lower case letters stand for the amino acids indicated in accordance with the pattern definition key table set forth in Figure 3. Figure 6 identifies preferred pattern sequences for constituting the finger 1, heel, and finger 2 regions of biosynthetic constructs of the invention. The dashes (-) indicate a peptide bond between adjacent amino acids. The SEQ ID NOS for the subgroup patterns are as follows: TGF-β subgroup pattern finger 1 (residues 1-34 of SEQ ID NO:64); TGF-β subgroup pattern heel (residues 35-64 of SEQ ID NO:64); TGF-β subgroup pattern finger 2 (residues 65-98 of SEQ ID NO:64); Vg/dpp subgroup pattern finger 1 (residues 1-34 of SEQ ID NO:65); Vg/dpp subgroup pattern

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heel (residues 35-68 of SEQ ID NO:65); Vg/dpp subgroup pattern finger 2 (residues 69-104 of SEQ ID NO:65); GDF subgroup pattern finger 1 (residues 1-34 of SEQ ID NO:66); GDF subgroup pattern heel (residues 35-72 of SEQ ID NO:66); GDF subgroup pattern finger 2 (residues 73-107 of SEQ ID NO:66); Inhibin subgroup pattern finger 1 (residues 1-34 of SEQ ID NO:67); Inhibin subgroup pattern heel (residues 35-71 of SEQ ID NO:67); Inhibin subgroup pattern finger 2 (residues 72-109 of SEQ ID NO:67).

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On pages 25-26, replace the brief description of figures 7(A)-(J) with the following:

Figure 7(A) shows the nucleotide (SEQ. ID NO: 90) and corresponding amino acid (SEQ. ID NO: 89) sequences of H2487, a modified OP-1 comprising N-terminal decapeptide collagen binding site inserted upstream of the seven-cysteine domain.

Figure 7(B) shows the nucleotide (SEQ ID NO: 92) and corresponding amino acid (SEQ. ID NO: 91) sequences of H2440, a modified OP-1 comprising a hexa-histidine domain attached 35 residues upstream of the first cysteine in the seven-cysteine domain.

Figure 7(C) shows the nucleotide (SEQ ID NO: 93) and amino acid (SEQ. ID NO: 94) sequences of H2521, a modified OP-1 comprising an FB leader domain of protein A attached 15 residues upstream of the first cysteine in the seven-cysteine domain.

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Figure 7(D) shows the nucleotide (SEQ ID NO: 95) and amino acid (SEQ. ID NO: 96) sequences of H2525, a modified OP-1 comprising both an FB leader domain of protein A and a hexa-histidine domain.

Figure 7(E) shows the nucleotide (SEQ ID NO: 97) and amino acid (SEQ. ID NO: 98) sequences of H2527, a modified OP-1 comprising an FB leader domain, a hexa-histidine domain, and an ASP-PRO acid cleavage site.

Figure 7(F) shows the nucleotide (SEQ ID NO: 99) and amino acid (SEQ. ID NO: 100) sequences of H2528, a modified CDMP-3 comprising an FB leader domain and a hexa-histidine domain.

Figure 7(G) shows the nucleotide (SEQ ID NO: 101) and amino acid (SEQ. ID NO: 102) sequences of H2469, a modified OP-1 (truncated) comprising 14 original residues upstream of the first cysteine in the conserved seven-cysteine domain.

Figure 7(H) shows the nucleotide (SEQ ID NO: 103) and amino acid (SEQ. ID NO: 104) sequences of H2510, a modified OP-1 comprising a collagen binding site inserted 7' residues upstream of the first cysteine in the conserved seven-cysteine domain.

Figure 7(I) shows the nucleotide (SEQ ID NO: 105) and amino acid (SEQ. ID NO: 106) sequences of H2523, a modified OP-1 comprising a collagen peptide and a spacer added 13 residues upstream from the first cysteine in the conserved seven-cysteine domain.

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Figure 7(J) shows the nucleotide (SEQ ID NO: 107) and amino acid (SEQ. ID NO: 108) sequences of H2524, a modified OP-1 comprising a hexa-histidine domain, a collagen peptide and a spacer added 13 residues upstream from the first cysteine in the conserved seven-cysteine domain.

On page 26, replace the brief description of figure 8 with the following:

Figure 8 is a restriction map encoding the OP-1 C-terminal seven cysteine active domain. The DNA sequence corresponds to nucleotides 1036-1341 of SEQ ID NO: 38. The protein sequence corresponds to amino acid residues 330-431 of SEQ ID NO: 39.

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On page 27, replace the brief description of figure 15 with the following:

Figure 15 shows the amino acid sequences for the finger 2 subdomain of various OP-1 mutants and their folding efficiencies and biological activities in the ROS cell based alkaline phosphatase assay. OP-1 (residues 393-431 of SEQ ID NO: 39); 2421 (SEQ ID NO: 109); 2406 (SEQ ID NO: 110); 2410 (SEQ ID NO: 111); 2247 (SEQ ID NO: 112); 2234 (SEQ ID NO: 113); 2233 (SEQ ID NO: 114); 2418 (SEQ ID NO: 115); 2443 (SEQ ID NO: 116); 2447 (SEQ ID NO: 117); 2457 (SEQ ID NO: 118); 2456 (SEQ ID NO: 119); 2460 (SEQ ID NO: 120); 2449 (SEQ ID NO: 121); 2467 (SEQ ID NO: 122) and 2464 (SEQ ID NO: 123).

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On page 76, replace the last paragraph with the following:

The mutant proteins of the present invention exhibit improved biological activity as well as extended half-life. Further, increased activity observed with the truncated proteins of the present invention may be due to elimination of basic residues and/or the lowering of the protein's isoelectric point. Biological activity and improved refolding can be enhanced when the modified proteins of the present invention are combined with the modifications described in copending applications [Atty Docket No. STK-076, USSN 09/374,958, filed on August 16, 1999] and [Atty Docket No. STK-077, USSN 09/374,936, filed on August 16, 1999], the disclosures of which are incorporated herein by reference.

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On page 80, replace the first full paragraph with the following:

E.coli expression for construction of heterodimers of the present invention is preferred, because the practitioner can adjust the ratio of each

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monomer for optimal yields of heterodimer. In addition, this method is very rapid. For example, in an *in vitro* heterodimer formation experiment between the hexa-histidine tagged OP-1, modified with the preferred modifications of charged amino acids, E, D, E, and R, (H2440) (see, for example, Attorney Docket No. STK-076, USSN 09/374,958, the entire disclosure of which is incorporated by reference herein) and BMP-2, the yield of heterodimers were excellent. There is an exceptionally high yield of heterodimer, more than the theoretically expected 50% heterodimer and 25% of each homodimer. This may occur because BMP-2 associates more readily with OP-1 than with itself, or faster than OP-1 reassociates with itself. Alternatively, the BMP-2 may act as chaperone for folding. Another experiment also showed heterodimer formation between BMP-2 and the H2447 mutant, OP-1 (no hexa-his tag), which also associated readily, generating good yields of heterodimer. Heterodimers were also made between FB-OP-1 (H2521) and BMP-2. Heterodimers of truncated OP-1, H2469 (retaining 15 residues upstream of the first cysteine), and BMP-5 (H2475); and H2469 and CDMP-2 (H2471) have also been constructed.

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On page 95, replace the paragraph immediately after the heading "EXAMPLE 9. Activity of 'domain swapping' mutant" with the following:

Domain swapping occurs, for example, when one takes the N-terminal region of one type of TGF-β family member protein and attaches it to the seven cysteine domain of another type of TGF-β family member protein. A mutant construct was created by splicing the sequence of the BMP-2 terminus onto the seven cysteine active domain of OP-1 using routine techniques generally known to those of ordinary skill in the art. The resulting mutant,

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